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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/738,599 | 12/15/2000 | Lisa K. Nolan | 255.0001 0122 | 1240 |

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| EXAMINER | |
|---|---|
| DEVI, SARVAMANGALA J N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

DATE MAILED: 01/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/738,599 | NOLAN ET AL. | |
| | Examiner | Art Unit | |
| | S. Devi, Ph.D. | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *30-33,35-42 and 44-73* is/are pending in the application.

4a) Of the above claim(s) *35, 36 and 46-66* is/are withdrawn from consideration.

5)☐ Claim(s) *30-33 and 69* is/are allowed.

6)☒ Claim(s) *37-42,67,68 and 70-73* is/are rejected.

7)☒ Claim(s) *44 and 45* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

# RESPONSE TO APPLICANTS' AMENDMENT

## Applicants' Amendment

**1)** Acknowledgment is made of Applicants' amendment filed 11/10/05 in response to the non-final Office Action mailed 08/10/05.

## Status of Claims

**2)** Claims 70, 71 and 73 have been amended via the amendment filed 11/10/05.

Claims 30-33, 35-42 and 44-73 are pending.

Claims 30-33, 37-42, 44, 45 and 67-73 are under examination.

## Prior Citation of Title 35 Sections

**3)** The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

## Prior Citation of References

**4)** The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

## Rejection(s) Withdrawn

**5)** The rejection of claim 70 made in paragraph 11 of the Office Action mailed 07/30/04 and maintained in paragraph 17 of the Office Action mailed 01/27/05 and paragraph 7 of the Office Action mailed 08/10/05 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is withdrawn in light of Applicants' amendment to the claim.

**6)** The rejection of claim 70 made in paragraph 12(a) of the Office Action mailed 07/30/04 and maintained in paragraph 18 of the Office Action mailed 01/27/05 and paragraph 8 of the Office Action mailed 08/10/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

**7)** The rejection of claims 37-40, 67 and 68 made in paragraph 19 of the Office Action mailed 08/10/05 under 35 U.S.C § 103(a) as being unpatentable over Barondess *et al.* (*Nature* 344: 871-874, 1990, already of record) (Barondess, 1990) in view of Harlow *et al.* (*In*: *Antibodies*: *A*

*laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, already of record), is withdrawn.

**8)** The rejection of claim 41 made in paragraph 20 of the Office Action mailed 08/10/05 under 35 U.S.C § 103(a) as being unpatentable over Barondess *et al.* (*Nature* 344: 871-874, 1990, already of record) (Barondess *et al.*, 1990) as applied to claim 37 above and further in view of Applicants' admitted state of the prior art, is withdrawn.

**9)** The rejection of claim 42 made in paragraph 21 of the Office Action mailed 08/10/05 under 35 U.S.C § 103(a) as being unpatentable over Barondess *et al.* (*Nature* 344: 871-874, 1990, already of record) (Barondess *et al.*, 1990) as applied to claim 38 above and further in view of Krieg *et al.* (WO 96/02555, already of record), is withdrawn.

## Rejection(s) Maintained

**10)** The rejection of claims 71-73 made in paragraph 16 of the Office Action mailed 08/10/05 under 35 U.S.C § 112, first paragraph, as containing new subject matter, is maintained for reasons set forth therein and herebelow.

Applicants cite MPEP § 2163(I)(B) and state that while there is no in *haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure. Applicants state that the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention now claimed. Applicants submit that the Office has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an Applicants' disclosure a description of the invention defined by the claims. Applicants allege that the Office has not provided reasons that amount to a preponderance of evidence as to why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. Applicants further allege that no *prima facie* case has been established. Applicants however acknowledge that a reason was offered by the Office for the lack of adequate description, and further cite the reason provided by the Office. Applicants now point to page 47, line 1 through page 48, line 17, and Example 5 of the specification, and request the Office to consider the disclosures therein.

Applicants' arguments have been carefully considered, but are not persuasive. As Applicants acknowledge themselves, the reasoning for the rejection was provided in the previous Office Action. It was stated that no descriptive support was found in specific pages/lines of the originally filed specification for the subject matter claimed in the instant claims. A review of parts of the specification now pointed to by Applicants indicates that Example 5 and pages 47 and 48 of the specification do not provide descriptive support for the subject matter claimed in the instant claims. Example 5 describes transformation of a bacterial cell with an *E. coli Iss* genetic material. Example 5 does not show that Applicants were in possession of an immunogenic composition comprising an isolated nucleic acid molecule comprising nucleotides 73 to 309 of the nucleotide sequence of SEQ ID NO: 22 and operably linked to 'a eukaryotic promoter' and expressing a polypeptide comprising an avian *E. coli* Iss polypeptide or an immunogenic fragment or immunogenic subunit thereof in an 'animal cell'. As of the filing date of the instant disclosure, Applicants were not in possession of an 'animal cell' comprising a 'eukaryotic promoter' wherein the 'animal cell' expressed a polypeptide comprising an avian *E. coli* Iss polypeptide or an immunogenic fragment or immunogenic subunit thereof. A generic remark of 'the appropriate type of cell', or an exemplification of a specific 'avian cell' in the specification (see lines 5-7 of page 48) does not provide explicit, implicit or inherent support for the broad limitation in the claim 'animal cell'. It is self-explanatory that an 'avian cell' is not identical in scope with an 'animal cell'. The limitation 'animal cell' encompasses a cell that is other than an avian cell, for which there is no descriptive support in the instant specification, as originally filed. Similarly, the term 'Pcmv' in the specification (see Figure 6 description on page 9) does not provide explicit, implicit or inherent support for the full scope of the limitation 'eukaryotic promoter', because the limitation 'eukaryotic promoter' encompasses promoters other than 'Pcmv'. The rejection stands.

**11)** The rejection of claims 71 and 73 made in paragraph 17(a) of the Office Action mailed 08/10/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants state that they have amended the claim to conform to the phrase regarding the immunogenic fragments used in claims 37 and 68.

Applicants' argument has been carefully considered, but is not persuasive. No amendment has been made by Applicants to claims 71 and 73. The rejection stands.

**12)** The rejection of claim 73 made in paragraph 17(b) of the Office Action mailed 08/10/05 under 35 U.S.C § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein and herebelow.

Applicants state that they have amended the claim to conform to the phrase regarding the immunogenic fragments used in claims 37 and 68.

Applicants' argument has been carefully considered, but is not persuasive. No amendment has been made by Applicants to claim 73. The rejection stands.

## Rejection(s) under 35 U.S.C § 112, Second Paragraph

**13)** Claim 71 is rejected under 35 U.S.C § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Claim 71 has improper antecedent basis in the limitation: '**the** polypeptide comprising an avian *E. coli Iss* ....' [Emphasis added]. Claim 71 depends from claim 69, which does not recite a 'polypeptide' in the claim.

## Rejection(s) under 35 U.S.C § 102

**14)** Claims 37-40 and 67 are rejected under 35 U.S.C § 102(b) as being anticipated by Barondess *et al.* (*Nature* 344: 871-874, 1990, already of record) (Barondess, 1990) as evidenced by Harlow *et al.* (*In*: *Antibodies*: *A Laboratory Manual*. Cold Spring Harbor Laboratory, Chapter 5, p. 76, 1988, already of record) and Hunter (US 5,554,372).

It is noted that lines 1 and 2 of page 49 of the specification define an 'immunogenic subunit of an *E. coli* Iss polypeptide' as 'a subunit that elicits an immune response in a subject to which it is administered'. At paragraph bridging pages 7 ad 8, 'an immunogenic composition' comprising a nucleic acid molecule encoding an *E. coli* Iss polypeptide is described as one which on 'administration to a subject induces the production of antibodies to said polypeptide'. It is further noted that 'a polypeptide' or 'an avian *E. coli* Iss polypeptide' as recited in claims 37 and 69 lacks a structure limit or a precise size limit.

Barondess *et al.* (1990) disclosed an isolated nucleic acid molecule comprising several

long stretches of contiguous nucleotides showing 100% sequence identity with nucleotides 73 to 309 of SEQ ID NO: 22, as well as plasmids, vectors, phages, and *E. coli* K12 host cells comprising the same. See the sequence search reports attached to the Office Action mailed 08/10/05; and Figure 1 of Barondess *et al.* (1990). Barondess *et al.* (1990) taught an isolated *bor* gene sequence which encodes an envelope protein, gene fusions, fragments thereof, and fusions expressed in lysogens or *E. coli* K12 host cells (see pages 871-873; Table 1; Fig 1; and Figure 1 legend). The fusion fragments were subcloned and sequenced. The fact that Barondess' polypeptide fragment or subunit was expressed or encoded indicates that Barondess' nucleic acid molecule further comprised a regulatory sequence, a control sequence, or a promoter operably linked to the nucleotide sequence. Due to the 100% sequence identity between Applicants' Iss polypeptide fragment or subunit and Barondess' expressed KTVDAAKICGGAENVVKTETQQTFVNGLLGFIT sequence, the prior art product is expected to generate an antibody response against the polypeptide when administered to a subject, because the art recognizes that the smallest peptides that elicit antibodies which bind to the original full-length protein are 6 amino acids in length. See the first sentence under 'Size of the Peptide' on page 76 of Harlow *et al.* Furthermore, the prior art *E. coli* host cell expressing the Iss polypeptide fragment or subunit, KTVDAAKICGGAENVVKTETQQTFVNGLLGFIT, inherently contains *E. coli* lipopolysaccharide, which lipopolysaccharide is known in the art to serve as an intrinsic adjuvant (i.e., pharmaceutically acceptable carrier). For example, Hunter taught that gram negative bacterial lipopolysaccharides serve as immunomodulating agents and immunologic adjuvants (see first sentence under Example 17 of Hunter). Clearly, the prior art *E. coli* host cell expressing the *Iss* polypeptide fragment or subunit, KTVDAAKICGGAENVVKTETQQTFVNGLLGFIT and comprising the endogenous lipopolysaccharide adjuvant serves as an immunogenic composition and anticipates the instantly claimed product. The Office's position that the polypeptide fragment KTVDAAKICGGAENVVKTETQQTFVNGLLGFIT encoded by the prior art product is the same as the Applicants' Iss polypeptide fragment is based upon the fact that every structural characteristic overlapping in the prior art polypeptide fragment and the Applicants' disclosure are the same. Since the polypeptide fragment encoded by the prior art nucleic acid molecule

contained in the host cell is structurally the same as the Iss polypeptide fragment or subunit recited in the instant claims, the prior art product is expected to have the intrinsic ability to generate an antibody response against the polypeptide when administered to a subject. The ability to generate an antibody response against the polypeptide when administered to a subject as recited in claim 67 is an intrinsic function inseparable from the prior art *E. coli* comprising the *bor* nucleic acid molecule and expressing the KTVDAAKICGGAENVVKTETQQTFVNGLLGFIT sequence.

Claims 37-40 and 67 are anticipated by Barondess *et al.* (1990). Harlow *et al.* or Hunter is **not** used as a secondary reference in combination with Barondess *et al.* (1990), but rather is used to show that every element of the claimed subject matter is disclosed by Barondess *et al.* (1990), with the unrecited limitation(s) being inherent in view of what is known in the art as explained above. See *In re Samour* 197 USPQ 1 (CCPA 1978).

## Rejection(s) under 35 U.S.C § 103

**15)** Claim 41 is rejected under 35 U.S.C § 103(a) as being unpatentable over Barondess *et al.* (*Nature* 344: 871-874, 1990, already of record) (Barondess *et al.*, 1990) as applied to claim 37 above and further in view of Applicants' admitted state of the prior art.

The teachings of Barondess *et al.* (1990) are explained above which do not expressly disclose that the polypeptide was expressed in an animal cell.

However, the expression of an art-known nucleic acid molecule via an art-known regulatory or control sequence that causes expression in an art-known animal cell line was routine and conventional in the art at the time of the invention. For instance, Applicants acknowledge in the instant specification the following to be known in the art: transformation and transfection methods; a wide variety of control or promoter sequences, compatible vectors, and eukaryotic expression systems or cell lines known to those skilled in the art of molecular biology to express polynucleotides; the use of vaccinia recombinant plasmid; the production of fusion protein for easy purification; and the standard affinity chromatography and purification methods. See pages 28-34 of the specification.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to express Barondess' (1990) isolated nucleic acid molecule or

polynucleotide via any one of the admittedly art-known animal or mammalian cell using any one of the admittedly art-known compatible control or regulatory sequences or eukaryotic promoters using art known techniques to produce the instant invention, with a reasonable expectation of success. Expression of Barondess' (1990) nucleic acid via an animal cell is well within the realm of routine experimentation. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of improved expression of Barondess' polynucleotide since improved expression is ideally desired in the art.

Claim 41 is *prima facie* obvious over the prior art of record.

**16)** Claims 42 and 68 are rejected under 35 U.S.C § 103(a) as being unpatentable over Barondess *et al.* (*Nature* 344: 871-874, 1990, already of record) (Barondess *et al.*, 1990) as applied to claim 38 above and further in view of Krieg *et al.* (WO 96/02555, already of record).

The teachings of Barondess *et al.* (1990) are explained above, which do not disclose the their polynucleotide to be further comprising an immunostimulatory sequence.

However, the use of immunostimulatory sequences, for example, an immunostimulatory oligonucleotide sequence along with a heterologous polynucleotide sequence, for the purpose of immunostimulation was well known in the art at the time of the invention. For instance, Krieg *et al.* showed that it was routine and conventional in the art to use a CpG immunostimulatory nucleotide sequence in a pharmaceutical composition (see abstract; and claims).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to express Barondess' (1990) nucleic acid molecule together with Krieg's immunostimulatory oligonucleotide sequence to produce the instant invention with a reasonable expectation of success. Given Krieg's teaching of the routine and conventional nature of using an immunostimulatory oligonucleotide in a pharmaceutical composition for the purpose of immunostimulation, one of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of further enhancing the immune response to Barondess' (1990) product.

Claims 42 and 68 are *prima facie* obvious over the prior art of record.

## Remarks

**17)** Claims 37-42, 67, 68 and 70-73 stand rejected. Claims 30-33 and 69 contain allowable

subject matter. Claims 44 and 45 are objected to for being dependent from a rejected claim.

**18)** Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (571) 273-8300.

**19)** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**20)** Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

January, 2006

S. DEVI, PH.D.
PRIMARY EXAMINER